2 Immediate postoperative radiotherapy in residual nonfunctioning pituitary adenoma: beneficial effect on local control without additional negative impact on pituitary function and life expectancy

Alfons C.M. van den Bergh, M.D.[1]; Gerrit van den Berg, M.D., Ph.D.[2]; Michiel A. Schoorl, M.D.[1]; Wim J. Sluiter, Ph.D.[2]; Anton M. van der Vliet M.D.[3]; Eelco W. Hoving, M.D. Ph.D.[4]; Ben G. Szabó M.D., Ph.D.[1]; Johannes A. Langendijk M.D., Ph.D.[1]; Bruce H.R. Wolffenbuttel, M.D., Ph.D.[2]; Robin P.F. Dullaart, M.D., Ph.D.[2]

1 Departments of Radiation Oncology, 2 Endocrinology, 3 Radiology, 4 Neurosurgery, University Medical Center Groningen, Groningen, the Netherlands.

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Abstract

Purpose To demonstrate the benefit of immediate postoperative radiotherapy in residual nonfunctioning pituitary adenoma (NFA) in perspective to the need for hormonal substitution and life expectancy.

Methods and Materials Retrospective cohort analysis of 122 patients, operated for NFA between 1979 and 1998. Recurrence was defined as regrowth on computed tomography or magnetic resonance imaging. The occurrence of hormonal deficiencies was defined as the starting date of hormonal substitution therapy.

Results Seventy-six patients had residual NFA after surgery and received immediate postoperative radiotherapy (Group 1); three patients developed a recurrence, resulting in a 95% local control rate at 10 years. Twenty-eight patients had residual NFA after surgery, but were followed by a wait-and-see policy (Group 2). Sixteen developed a recurrence, resulting in a local control rate of 49% at 5 years and 22% at 10 years ($p<0.001$ compared with Group 1). There were no differences between Group 1 and 2 regarding the need for substitution with thyroid hormone, glucocorticoids, and sex hormones before first surgery, directly after surgery and at end of follow-up. There were no differences in hormone substitution free survival between Group 1 and Group 2 during the study period after first surgery. Life expectancy was similar in Group 1 and 2, and their median life expectancy did not differ from median life expectancy in the general population.

Conclusions Immediate postoperative radiotherapy provides a marked improvement of local control among patients with residual NFA compared to surgery alone, without an additional deleterious effect on pituitary function and life expectancy.

Introduction

Pituitary adenomas are benign lesions comprising 10-15% of all intracranial tumours. Approximately 25% of all pituitary adenomas are clinically nonfunctioning (NFA). An incidence of 10 cases per million per year of NFAs is estimated[1]. Most patients present with symptoms at middle age, because of slow growth and absence of symptoms of hormonal hypersecretion[2]. This explains why NFAs are frequently macroadenomas with extension outside the sellar region.

As NFAs usually present with signs resulting from local mass effect, such as bitemporal hemianopsia, decreased visual acuity, and hypopituitarism, whereas patients quality of life may be impaired.

In contrast to other pituitary adenomas such as prolactinoma and growth hormone secreting adenomas, NFAs in general do not respond well to medical treatment[3]. Therefore, the treatment of choice is either transsphenoidal or transcranial surgery, aiming at complete tumour removal or decompression of surrounding structures only. Because of the invasive character of larger pituitary adenomas, with infiltration of the neighbouring structures such as arachnoid membrane, dura, sinus cavernosus and the skull base, complete surgical removal is frequently not achieved[4].

Recent studies show a higher progression free survival rate for surgery plus adjuvant radiotherapy compared to surgery alone in patients with residual postoperative NFA[5,6].

More frequent anterior pituitary dysfunction[7], radiation optic neuropathy[8], cerebrovascular disease[9-13], and the induction of secondary tumors[14,15] are proposed to be adverse sequelae of radiotherapy.

This cohort study was initiated to evaluate the role of radiotherapy on local control in perspective to the need for hormonal substitution therapy, other potential side effects, and life expectancy in patients with NFAs.

Methods and materials

Patients

Radiologic, neurosurgical, endocrinological and radiotherapy records of all patients (*N* = 131) with a NFA who were operated upon at the University Medical Center Groningen between 1979 and 1998 were reviewed. All patients had histologically and endocrinologically verified NFAs. Nine out of 131 patients were not included in this series because they were lost to follow-up. The remaining 122 patients were included in the analysis.

The study population consisted of three distinctive groups:

Group 1 consisted of 76 patients (62%) with radiologic evidence of residual NFA, who received immediate postoperative radiotherapy after the first operation. Twenty-six of these

patients were operated transcranially (34%) and 50 by the transsphenoidal route (66%) (see Table 1). The median time between surgery and the start of radiotherapy was 5.8 months; it is just possible to decide on computed tomography (CT)/magnetic resonance imaging (MRI), performed 3 to 4 months after operation, if there is residual pituitary adenoma, because mass effects due to operation have disappeared after that time period. The median follow-up time between radiotherapy and last MRI was 93 (range, 14 - 248) months.

Group 2 consisted of 28 patients (23%) with radiologic residual NFA after neurosurgery in which the consultant endocrinologist decided for a wait-and-see policy. Twenty-one of these patients (75%) underwent a transsphenoidal procedure while in 7 patients (25%) a craniotomy was performed (see Table 1). The median follow-up time between operation and last MRI was 71 (range, 3 - 206) months.

Group 3 consisted of 18 patients (15%; 12 after transsphenoidal surgery and 6 after craniotomy) without radiologic evidence of residual NFA after surgery. Three patients in this group received immediate postoperative radiotherapy.

Radiotherapy

All patients in Group 1 were treated with linear accelerators with 4-18 MV photons. A two-field opposed lateral technique was used in 10 patients, a three-field technique in 25 patients, a five-field technique in 14 patients, a combination of these techniques in 25 patients, and a rotation technique in 2 patients. In the time period 1985 to 1990, the radiation dose to the tumor was prescribed at the tumor encompassing isodose. From 1991 to 1998, it was prescribed at a central point in the tumor according to the recommendations of the International Commission on Radiation Units and Measurements (ICRU)[16]. Total radiation dose ranged from 45.0 to 55.8 Gray (Gy). The daily radiation fraction size varied from 1.8 to 2.0 Gy. The median overall treatment time was 35 days (range, 30 - 42 days). The radiation fraction schemes used were 45 Gy in 25 daily fractions (n = 44; 58%), 50 Gy in 25 daily fractions (n = 19; 25%), 50.4 Gy in 28 daily fractions (n = 7; 9%), 46 Gy in 23 daily fractions (n = 5; 7%), and 55.8 Gy in 31 daily fractions (n = 1; 1%). All radiation treatment fields were applied daily, 5 times a week.

Progression and hormonal evaluation

Progression was defined as recurrence of completely resected or regrowth of residual NFA on CT or MRI. The occurrence of hormonal deficiencies was defined as the starting date of hormonal substitution therapy. Thyroid hormone and androgen deficiency were diagnosed by subnormal serum FT4 and testosterone levels, respectively. In premenopausal women, sex hormone deficiency was diagnosed by amenorrhea and low serum estradiol levels. In women aged above 50 years, as an indication of postmenopausal status, sex hormone deficiency was not classified. In women using estrogens/progestagens for contraceptive reasons, sex hormone deficiency was also not classified. Glucocorti-

Table 1 Patient characteristics, treatment data, and anterior pituitary hormone substitutions in Group 1 (immediate postoperative radiotherapy) and Group 2 (wait-and-see policy)

	Group 1 (*n* = 76)	Group 2 (*n* = 28)	*p*-value
Age (years)	53 (17-75)	53 (12-79)	0.75
Sex: M/F	45/31	14/14	0.54
Preoperative hormonal substitutions			
Thyroxin	21 of 76 (28%)	5 of 28 (18%)	0.51
Glucocorticoids	17 of 76 (22%)	4 of 28 (14%)	0.57
Sex hormones	7 of 61*(11%)	0 of 21*(0%)	0.29
Number of preoperative hormonal substitutions per patient	0: 45 (59%) 1: 18 (24%) 2: 11 (14%) 3: 2 (3%)	0: 21(75%) 1: 5 (18%) 2: 2 (7%) 3: 0	0.43
Surgery type: C/T	26/50	7/21	0.54
Hormonal substitutions directly after first surgery			
Thyroxin	39 of 76 (51%)	16 of 28 (57%)	0.77
Glucocorticoids	29 of 76 (38%)	14 of 28 (50%)	0.39
Sex hormones	28 of 61*(46%)	10 of 21 (48%)	0.91
Number of hormonal substitutions per patient directly after first surgery	0: 26 (34%) 1: 15 (20%) 2: 24 (32%) 3: 11 (14%)	0: 9 (33%) 1: 4 (14%) 2: 9 (32%) 3: 6 (21%)	0.81
Hormonal substitutions at end of FU			
Thyroxin	60 of 76 (79%)	20 of 28 (71%)	0.51
Glucocorticoids	56 of 76 (74%)	20 of 28 (71%)	0.38
Sexhormones	48 of 61*(79%)	15 of 21* (71%)	0.57
Number of hormonal substitutions per patient at end of FU	0: 7 (9%) 1: 11 (14%) 2: 21 (28%) 3: 37 (49%)	0: 6 (21%) 1: 3 (11%) 2: 6 (21%) 3: 13 (46%)	0.39

Abbreviations: M = male; F = female; C = craniotomy; T = transsphenoidal surgery; Ok = operation; Rt = radiotherapy; FU = follow-up; pts = patients.
Age in median years (range).
* In group 1, 15 of 31 women and in group 2, 7 of the 14 women were postmenopausal (age > 50 yrs) at time of first surgery; in these women sex hormone deficiency was not classified. None of the premenopausal women in each group used estrogens/progestagens for contraceptive reasons.

coid deficiency was diagnosed by a low serum cortisol, by an insufficient serum cortisol response to insulin-induced hypoglycemia, or by an insufficient urinary tetrahydro compound S excretion with cut-off criteria as described elsewhere[17,18]. Pituitary function was checked at least twice annually. Growth hormone substitution was introduced in our clinic in the mid-nineties; growth hormone deficiency was not taken into account in the hormonal evaluation.

Cerebrovascular disease was defined as any transient or permanent cerebrovascular disorder.

Statistical analysis

In univariate analysis, local control rate as well as hormone substitution free survival were estimated using the Kaplan Meier method. To test the statistical significant differences between survival curves, the log rank test was used. Data are given in median (range) or in percentages. Frequencies of hormone deficiencies were compared in Chi-square analysis.

Life expectancy was studied after transformation of survival time to standardized survival time (SST) to adjust for background mortality in the general population. SST is the quotient of observed survival time and median life expectancy in the general Dutch population matched for gender, age and year of operation. These life expectancies were derived from the data provided by the Dutch authorities (www.cbs.nl). The analytical background of this method has been reported elsewhere[19]. A two-sided p-value <0.05 was considered to be significant.

Results

Local Control Rate

Group 1. In three out of 76 patients (4%), progression was observed after a median interval of 23 (16, 23 and 104, respectively) months after surgery. Local control rate was 95% at 5 as well as at 10 years (Fig. 1). Local recurrence or regrowth was always intra/parasellar.

Group 2. In 16 out of 28 patients (57%), progression developed after a median interval of 30 (11-95) months. Local control rate was 49% and 22% at 5 and 10 years, respectively (Fig. 1). This was significantly worse than the local control rate among patients in Group 1 (p = 0.001). Fourteen of these 16 patients received "salvage" radiotherapy after a median interval of 38 months after the first neurosurgical procedure. Six patients received salvage radiotherapy immediately after diagnosis of regrowth, 7 patients after a second operation (4 craniotomy, 3 transsphenoidal procedure) and 1 patient after a third operation. All patients had residual NFA after repeated operation. The radiation fractionation schedules used were 45 Gy in 25 fractions (n = 13) and 50 Gy in 25 fractions (n = 1). Local control rate after salvage radiotherapy at 5 and 10 years after first operation was 95%. In 2 patients, salvage radiotherapy was not applied because of cerebral infarction in one and acute death shortly after diagnosis of progression in the other.

Group 3. In 1 patient (6%) a recurrence developed 15 months after neurosurgery; this patient was treated with radiotherapy.

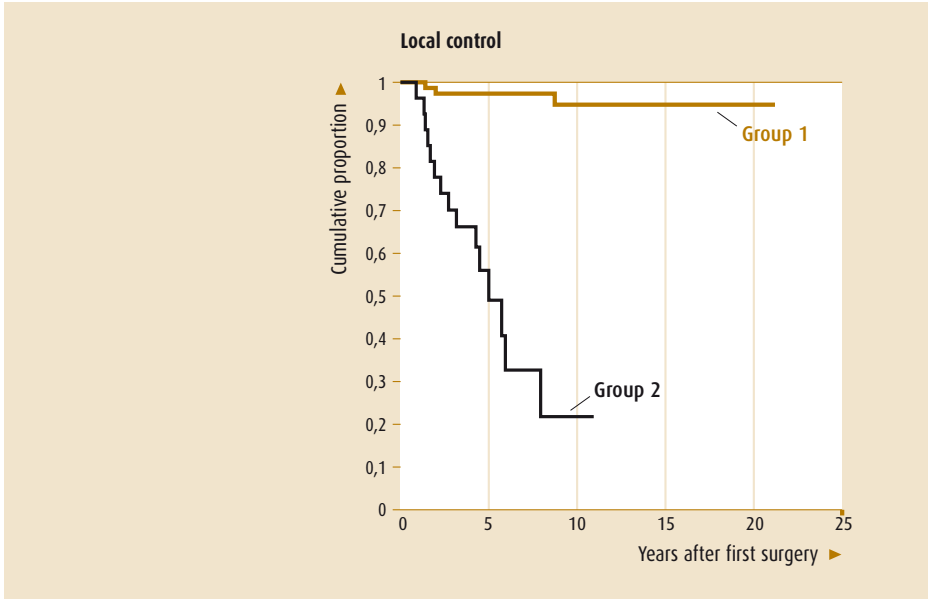

Figure 1 Kaplan Meier plot showing local control of residual non-functioning pituitary adenoma in Group 1 (after immediate postoperative radiotherapy), and in Group 2; (wait-and-see policy after first operation); $p = 0.001$ by log-rank test.

Hormonal substitution free survival

Preoperatively, no significant differences in anterior pituitary hormonal substitution were found between Group 1 and 2 (Table 1). Directly after first surgery, again, no differences were found regarding thyroid hormone-, glucocorticoid-, or sex hormone substitution between Group 1 and 2 (Table 1). At the end of follow-up, the need for hormonal substitution was also not different between the groups (Table 1). The number of hormone deficiencies per patient at diagnosis, directly after first surgery and at the end of follow-up was comparable between Group 1 and 2 (Table 1). As shown in Figure 2 - 4, there were no differences in hormone substitution free survival with respect to thyroid hormone, glucocorticoids, and sex hormones between the groups during the study period after first surgery.

Before surgery one patient in Group 1 and none in Group 2 had antidiuretic hormone deficiency. Postoperatively, an additional 6 patients in Group 1 and 2 patients in Group 2 required permanent vasopressin treatment. These numbers did not change until end of follow-up in either group ($p = 0.97$). Furthermore, the type of operation was not associated with vasopressin-substitution ($p = 0.99$).

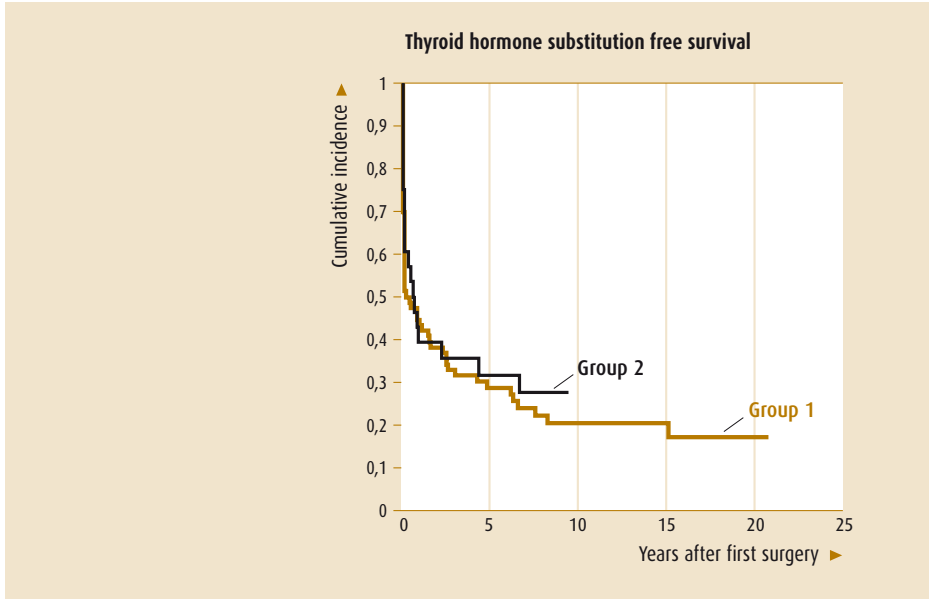

Figure 2 Kaplan Meier plot showing thyroid hormone substitution free survival after first surgery in Group 1 (immediate postoperative radiotherapy) and 2 (wait-and-see policy); $p = 0.94$ by log-rank test.

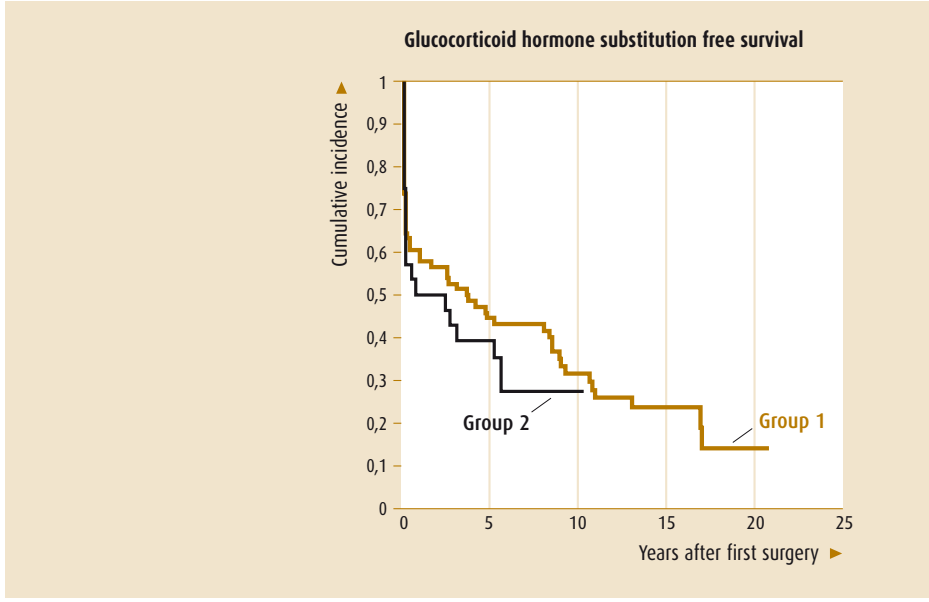

Figure 3 Kaplan Meier plot showing glucocorticoid hormone substitution free survival after first surgery in Group 1 (immediate postoperative radiotherapy) and 2 (wait-and-see policy) ; $p = 0.22$ by log-rank test.

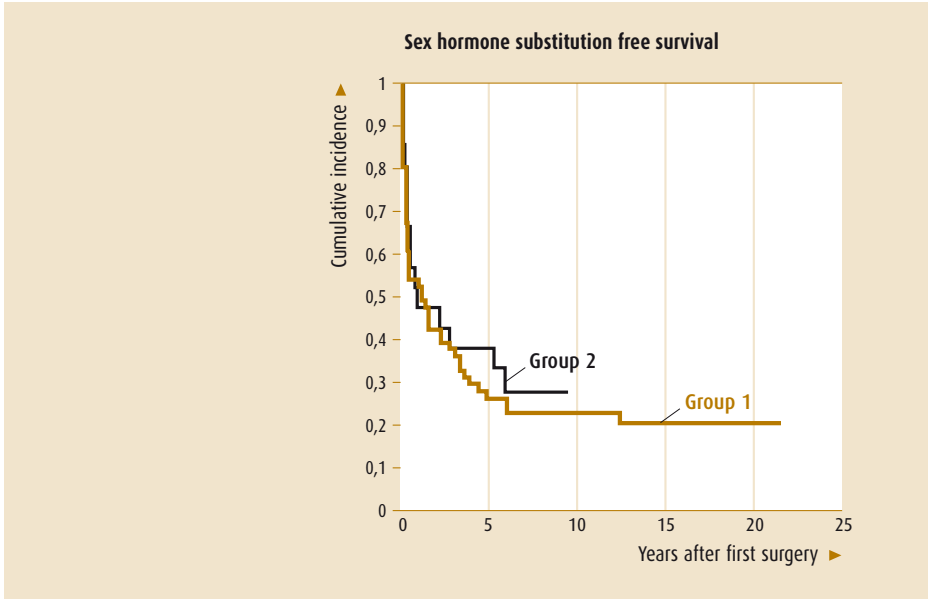

Figure 4 Kaplan Meier plot showing sex hormone substitution free survival after first surgery in Group 1 (immediate postoperative radiotherapy) and 2 (wait-and-see policy); $p = 0.41$ by log-rank test.

Cerebrovascular disease

No statistically significant difference with regard to the incidence of cerebrovascular disease was observed between Group 1 and 2 at diagnosis, after neurosurgery, and during follow-up (p = 0.12). In Group 1, one out of 76 patients suffered cerebrovascular disease before surgery and 13 patients between surgery and final follow-up. In Group 2, three out of 28 patients suffered cerebrovascular disease before surgery and four patients between first neurosurgery and final follow-up. Furthermore, no association was found between the type of surgery and cerebrovascular disease (p = 0.61).

Epilepsy

No statistically significant difference was found in prevalence of epilepsy between Group 1 and 2 at diagnosis, after neurosurgery, and during follow-up (p = 0.19). In Group 1 one out of 76 patients suffered epilepsy before surgery and 6 patients after neurosurgery until end of follow-up. In Group 2, none of the 28 patients suffered epilepsy. No significant association was found between the type of surgery and epilepsy (p = 0.47).

Tumor induction

In Group 1, 1 out of 76 patients was operated for a meningioma, localized right frontoparietal at a scar place, 14 years after a right-sided craniotomy and radiotherapy for a NFA. Although p53 staining of the meningioma tissue was negative, a relationship with radiotherapy cannot be excluded. In Group 2, 1 patient died due to a glioblastoma multiforme 1 year after surgery for NFA.

Overall survival and life expectancy

The overall survival was not different between Group 1 and 2 (Fig.5; p = 0.25). There was no effect of type of surgery on overall survival. Median standardised survival time was 0.97 (95% CI, 0.56-1.39) in Group 1 and 2 combined (Fig. 6). There is no difference from the expected value of 1.0 in the age and gender-matched general Dutch population.

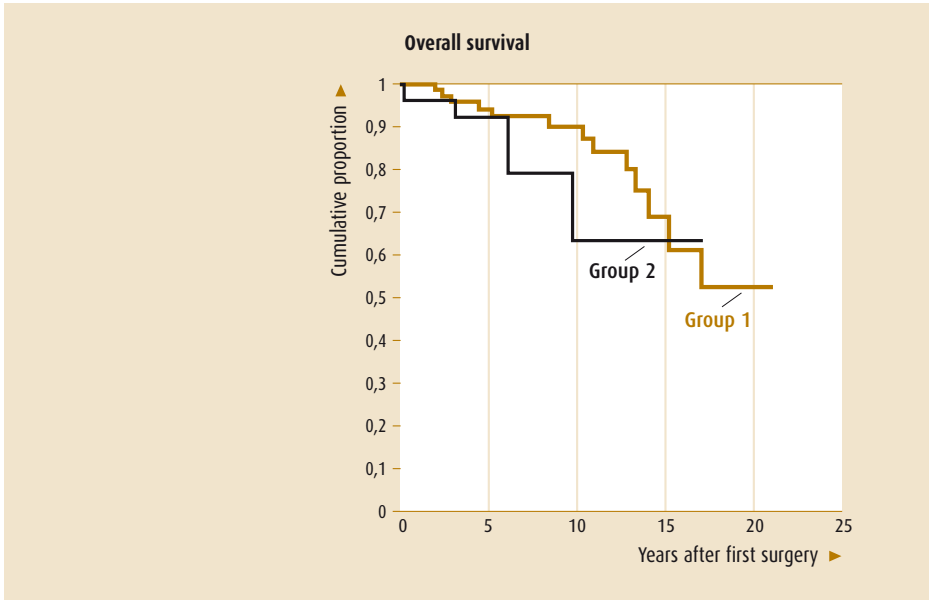

Figure 5 Kaplan Meier plot showing overall survival in Group 1 (immediate postoperative radiotherapy) in comparison with Group 2 (wait-and-see policy); $p = 0.25$ by log-rank test.

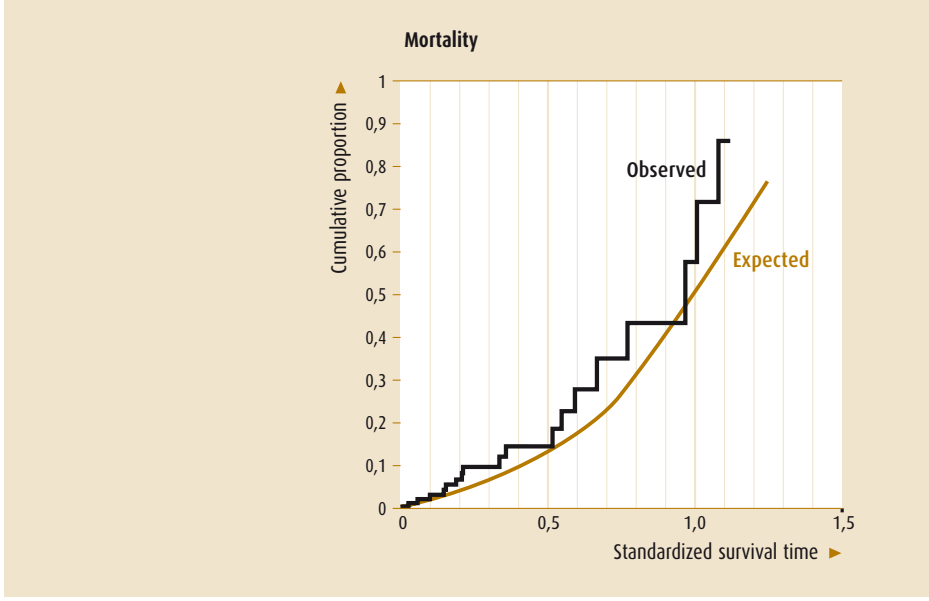

Figure 6 Observed cumulative death in our cohort (Group 1 and 2 combined; $n = 104$ patients) in perspective to the expected cumulative death in the age and gender matched normal population in The Netherlands; $p = 0.25$ by log-rank test

Discussion

In the present series of NFA patients, excellent local control (95% at 10 years) was achieved when immediate postoperative radiotherapy was applied in case of residual tumor. In comparison, local control was only 49% at 5 years and 22% at 10 years when a wait-and-see policy was followed. Importantly, immediate postoperative radiotherapy did not result in an additional need for conventional hormonal substitution treatment, or in an excess of epilepsy, cerebrovascular disease, and intracerebral malignancy in comparison to an expectant strategy. Furthermore, it is noteworthy that life expectancy was similar in both groups, and did not differ from the general Dutch population. Our survey thus suggests that immediate postoperative radiotherapy in case of residual NFA can be applied safely.

Local control rate after immediate postoperative radiotherapy reported here agrees with other studies, showing that 82% to 97% of patients remained free of tumor regrowth after 10 years of follow-up[5,6,20-22]. Comparable with our data, a local control rate of only 40% to 70% at 5 years and of 15% to 50% at 10 years was documented previously when a wait-and-see policy was followed[23-26]. Importantly, despite protocolized follow-up with serial MRIs, a symptomatic recurrence was observed in 4 of 34 prospectively followed patients after a period of only 28 months[27]. In agreement, symptomatic recurrences were recently reported to be present in 6% to 21% of patients[28]. In the present study, salvage radiotherapy in case of regrowth was deemed clinically necessary after a median interval of 38 months after first surgery in 50% (14/28) of NFA patients; in 7 patients after a second and in 1 patient even after a third operation. A wait-and-see policy can be expected to result in a higher frequency of MRI and an increased frequency of re-operations, which likely results in emotional and social dysfunction[29] as well as in additional health care costs. One should, therefore, be aware of the possible risks of an expectant policy in case of residual postoperative NFA.

A frequently used argument to postpone postoperative radiotherapy is the possible development of radiation-induced hypopituitarism[7]. This supposition is mainly based on the results from a small series of 35 patients[7]. In that report, 50% of patients had already pituitary hormonal deficiencies before radiotherapy, which increased to 75% after this treatment.

Patient characteristics at diagnosis and directly after surgery were similar in subjects with residual NFA who did and did not receive immediate postoperative radiotherapy in this series. It is of relevance, therefore, that our study clearly demonstrates that there was no difference in the need for thyroid hormone, glucocorticoids, sex-steroids, and vasopressin between the immediate postoperative radiotherapy group and the wait-and-see group with salvage radiotherapy. This lack of negative impact of immediate postoperative radiotherapy on pituitary function could not be attributed to

bias caused by differences in hormonal deficiencies before and shortly after surgery, or in clinical characteristics between the groups. A potential shortcoming of our study is that we did not evaluate the frequency of growth hormone replacement therapy in each group. Such an analysis was not done because this treatment was introduced relatively late in the time frame of our evaluation period. Moreover, it is very likely that many patients in each group already had growth hormone deficiency shortly after surgery, given the high frequency of other hormonal deficiencies[18,30].

Radiotherapy could result in other unwanted side effects. The possible negative effect of radiotherapy on the development of cerebrovascular disease is frequently mentioned but still debated[9,10,12,31]. In the present series, the risk for cerebrovascular disease was not different between groups. The induction of intracranial malignancies and meningiomas by radiotherapy is also debated[14,15]. In our cohort, no intracranial malignancies and one meningioma was diagnosed in a total of 90 irradiated patients. Another possible late side effect of radiation therapy is radiation optic neuropathy, but we have already documented that this is a very rare complication, provided fractionated radiotherapy is applied with a recommended total dose not exceeding 45 Gray in NFA patients[8].

In the present study, we did not evaluate the effect of radiotherapy on cognitive function and on quality of life. Previous studies have shown diminished cognitive function and impaired quality of life in newly diagnosed patients with NFA compared to healthy subjects[32,33]. A cross-sectional study demonstrated reduced cognition and some impairment in quality of life in a mixed group of patients with non-functioning and hormone secreting pituitary tumors who were treated with surgery and radiotherapy compared to patients who were treated with surgery alone[34]. Such an effect was not found in another report[35]. Furthermore, the contribution of postoperative radiotherapy to a possible decline in mental performance and quality of life is not well understood, because prospective data, which take the effects of both conventional pituitary hormone substitution and growth hormone replacement into account, are currently not available. Moreover, it can be expected that improvement in radiation treatment techniques will result in significantly lower radiation doses to the cerebral parenchyma[36], with an assumed sparing effect on cognitive function.

Several studies have addressed the question whether there is increased mortality in NFA patients, and to define the possible negative impact of radiotherapy on mortality in this patient category[31,37-39]. The interpretation of these data is difficult, because of inclusion of patients with hypopituitarism not due to NFA, the possible effect of (treated) deficiencies of conventional anterior pituitary hormones and anti-diuretic hormone, as well as the effect of growth hormone deficiency on mortality[39]. In the present series, log-rank analysis demonstrated that survival did not differ between patients, who received immediate post-operative radiotherapy and patients in whom a wait-and-see

policy was followed. When all NFA patients were combined, life expectancy was similar to that observed in the general age- and sex-matched population from the Netherlands. In comparison, increased mortality has been observed in several[31,37-39], but not in all surveys[40] comprising pituitary patients due to various causes. The largest series available so far shows a modest excess in overall mortality in NFA patients, without a significant independent adverse impact of radiotherapy[39]. Several factors such as differences in time frame of patient surveillance, with follow-up being starting as early as 1946 to 1958 in some previous reports[12] as well as the relatively low frequency of transcranial surgery and the lack of additional negative impact of radiotherapy on conventional pituitary hormone deficiencies in the present series, may explain part of the discrepancy.

In conclusion, immediate postoperative radiotherapy in case of residual NFA provides a marked long lasting improvement of local control among patients with residual non-functioning pituitary adenoma compared to surgery alone, without an additional deleterious effect on pituitary function and life expectancy. Therefore, results of this study support to perform immediate postoperative radiotherapy in this patient category. The present results also underscore that immediate postoperative radiotherapy is not necessary in apparently complete resected NFA.

References

1. OHalloran DJ, Shalet SM. Radiotherapy for pituitary adenomas: An endocrinologist's perspective. *Clin Oncol* 1996;8:79-84
2. Nobels FE, Kwekkeboom DJ, Herder WW de, *et al.* Klinisch niet-functionerende hypofyseadenomen; diagnostische mogelijkheden en therapeutische opties. [Clinically non-functioning hypophyseal adenomas; Diagnostic possibilities and therapeutic options]. *Ned Tijdschr Geneeskd* 1992;136:1148-1152
3. Sassolas G, Trouillas J, Treluyer C, *et al.* Management of nonfunctioning pituitary adenomas. *Acta Endocrinol (Copenh)* 1993;129(Suppl.):121-126
4. Rauhut F, Stuschke M, Sack H, Stolke D. Volume dependence of late effects after radiotherapy of invasive pituitary adenomas. In: Wiegel T, Hinkelbein W, Brock M, Hoell T, editors. *Controversies in Neuro-oncology. Frontiers of radiation therapy and oncology*. Basel: Karger;1999. p. 315-317
5. Gittoes NJL, Bates AS, Tse W, *et al.* Radiotherapy for non-functioning pituitary tumours. *Clin Endocrinol* 1998;48:331-337
6. Paek SH, Beverly Downes M, Bednarz G, *et al.* Integration of surgery with fractionated stereotactic radiotherapy for treatment of nonfunctioning pituitary macroadenomas. *Int J Radiat Oncol Biol Phys* 2005;61:795-808
7. Snyder PJ, Fowble BF, Schatz NJ, *et al.* Hypopituitarism following radiation therapy of pituitary adenomas. *Am J Med* 1986;81:457-462
8. van den Bergh ACM , Schoorl MA, Dullaart RP, *et al.* Lack of radiation optic neuropathy in 72 patients treated for pituitary adenoma. *J Neuroophthalmol* 2004;24:200-205
9. Flickinger JC, Nelson PB, Taylor F, Robinson A. Incidence of cerebral infarction after radiotherapy for pituitary adenoma. *Cancer* 1989;63:2404-2408
10. Brada M, Burchell L, Ashley S, Traish D. The incidence of cerebrovascular accidents in patients with pituitary adenoma. *Int J Radiat Oncol Biol Phys* 1999;45:693-698
11. Brada M, Ashley S, Ford D, *et al.* Cerebrovascular mortality in patients with pituitary adenoma. *Clin Endocrinol* 2002;57:713-717
12. Erfurth E, Bulow B, Svahn-Tapper G, *et al.* Risk factors for cerebrovascular deaths in patients operated and irradiated for pituitary tumors. *J Clin Endocrinol Metab* 2002;87:4892-4899
13. Erfurth E, Hagmar L. Cerebrovascular disease in patients with pituitary tumors. *Trends in Endocrinol and Metab* 2005;16:334-342
14. Erfurth E, Bulow B, Mikoczy Z, *et al.* Is there an increase in second brain tumours after surgery and irradiation for a pituitary tumour? *Clin Endocrinol* 2001;55:613-616
15. Minniti G, Traish d, Ashley S, *et al.* Risk of second brain tumour after conservative surgery and radiotherapy for pituitary adenoma: Update after further 10 years. *J Clin Endocrinol Metab* 2004;90:800-804

16. ICRU Prescribing, recording and reporting photon beam therapy. Report 50 1993, Bethesda, MD, USA.
17. Tjeerdsma G, Sluiter WJ, Hew JM, *et al.* Hyperprolactinaemia is associated with a higher prevalence of pituitary-adrenal dysfunction in non-functioning pituitary macroadenoma. *Eur J Endocr* 1996;135:299-308
18. Dullaart RP, Pasterkamp SH, Beentjes JA, Sluiter WJ. Evaluation of adrenal function in patients with hypothalamic and pituitary disorders; comparison of serum cortisol, urinary free cortisol and the human-corticotrophin releasing hormone test with the insulin tolerance test. *Clin Endocrinol* 1999;50:465-471.
19. Links TP, Tol KM van, Jager PL, *et al.* Life expectancy in differentiated thyroid cancer: A novel approach to survival analysis. *Endocr Relat Cancer* 2005;12:273-280
20. Brada M, Rajan B, Traish D, *et al.* The long-term efficacy of conservative surgery and radiotherapy in the control of pituitary adenomas. *Clin Endocrinol* 1993;38:571-578
21. Breen P, Flickinger JC, Kondziolka D, Martinez AJ.. Radiotherapy for nonfunctional pituitary adenoma: Analysis of long-term tumor control. *J Neurosurg* 1998;89:933-938
22. Chun M, Masko B, Hetelekidis S. Radiotherapy in the treatment of pituitary adenomas. *Int J Radiat Oncol Biol Phys* 1988;5:305-309
23. Sheline GE. Proceedings:Treatment of nonfunctioning chromophobe adenomas of the pituitary. *Am J Roentgenol Radium Ther Nucl Med* 1974;120:553-561
24. Jaffrain-Rea ML, Derome P, Bataini JP, *et al.* Influence of radiotherapy on long-term relapse in clinically non-secreting pituitary adenomas. A retrospective study (1970-1988). *Eur J Med* 1993;2:398-403
25. Park P, Chandler WF, Barkan AL, *et al.* The role of radiation therapy after surgical resection of nonfunctional pituitary macroadenomas. *Neurosurgery* 2004;55:100-107
26. Woollons AS, Hunn MK, Rajapakse YR, *et al.* Non-functioning pituitary adenomas: Indications for postoperative radiotherapy. *Clin Endocrinol* 2000;53:713-717
27. Soto-Ares G, Cortet-Rudelli C, Assaker R, *et al.* MRI protocol technique in the optimal therapeutic strategy of non-functioning pituitary adenomas. *Eur J Endocrinol* 2002;146:179-186
28. Benveniste RJ, King WA, Walsh J, *et al.* Repeated transsphenoidal surgery to treat recurrent or residual pituitary adenoma. *J Neurosurg* 2005;102:1004-1012
29. Andrewes DG, Kaye A, Murphy M, *et al.* Emotional and social dysfunction in patients following surgical treatment for brain tumour. *J Clin Neurosc* 2003;10:428-433
30. Toogood AA, Beardwell CG, Shalet SM. The severity of growth hormone deficiency in adults with pituitary disease is related to the degree of hypopituitarism. *Clin Endocrinol* 1994;41:511-516
31. Rosen T, Bengtsson B. Premature mortality due to cardiovascular disease in hypopituitarism. *Lancet* 1990;336:285-288.

32. Guinan EM, Lowy C, Stanhope N, *et al.* Cognitive effects of pituitary tumours and their treatments: Two case studies and an investigation of 90 patients. *J Neurol Neurosurg Psych* 1998;65:870-876
33. Peace KA, Orme SM, Padayatty SJ, *et al.* Cognitive dysfunction in patients with pituitary tumour who have been treated with transfrontal or transsphenoidal surgery or medication. *Clin Endocrinol* 1998;49:391-396.
34. Noad R, Narayanan KR, Howlett T, *et al.* Evaluation of the effect of radiotherapy for pituitary tumours on cognitive function and quality of life. *Clin Oncol* 2004;16:233-237
35. Wallymahmed ME, Foy P, MacFarlane IA. The quality of life of adults with growth hormone deficiency: Comparison with diabetic patients and control subjects. *Clin Endocrinol* 1999;51:333-338
36. Perks JR, Jalali R, Cosgrove VP, *et al.* Optimization of stereotactically-guided conformal treatment planning of sellar and parasellar tumors, based on normal brain dose volume histograms. *Int J Radiat Oncol Biol Phys* 1999;45:507-513
37. Bulow B, Hagmar L, Mikoczy Z, Nordstrom CH, Erfurth EM. Increased cerebrovascular mortality in patients with hypopituitarism. *Clin Endocrinol* 1997;46:75-81
38. Nilsson B, Gustavsson-Kadaka E, Bengtsson B, Jonsson B. Pituitary adenomas in Sweden between 1958 and 1991: Incidence, survival and mortality. *J Clin Endocrinol Metab* 2000;85:1420-1425
39. Tomlinson JW, Holden N, Hills RK, *et al.* Association between premature mortality and hypopituitarism. *Lancet* 2001;357:425-431
40. Bates AS, Bullivant B, Sheppard MC, Stewart PM. Life expectancy following surgery for pituitary tumours. Clin Endocrinol 1999;50:315-319